

Integrative Biomedical Sciences

Research Article

The Promising Role of Dynamic ^{18}F -NaF PET-CT in Diagnosing Symptomatic Joint Prosthesis

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Abstract

Our purpose was to establish proof of principle case study for the use of dynamic ^{18}F -NaF PET-CT in the assessment of knee and hip prostheses. Approval was granted by the research ethics committee and informed consent was obtained. This is a case study investigating the role of dynamic ^{18}F NaF PET-CT in a patient with bilateral knee prostheses (1 symptomatic/painful and 1 asymptomatic). Both knees were studied with dynamic ^{18}F -NaF PET-CT technique to demonstrate the different pattern of uptake in normal/asymptomatic joint as well as painful joints with aseptic loosening. In addition, a knee aspirate was obtained from the symptomatic knee and serum C-reactive protein and erythrocyte sediment rate levels as well as a peripheral white cell count were obtained in addition to 12 month clinical follow up. Images were obtained with multi-sequential dynamic image acquisition in list mode using GE Healthcare® volume imaging protocol (ViP) after an intravenous injection of 250 MBq ^{18}F -NaF. The images were interpreted as normal, loosening or septic loosening based on the graphical pattern of tracer uptake produced at the bone-prosthesis interface. A final diagnosis was made by a combination of joint aspiration microbiology and clinical follow-up for 1 year; in addition to C-reactive protein and erythrocyte sediment rate levels as well as peripheral white cell count. NaF PET results were compared with 3-phase dynamic bone scan results and plain radiographs. The degree of uptake in the symptomatic joint exceeded background levels and also levels of uptake in the asymptomatic knee. The pattern of uptake and curve slope in both the asymptomatic and symptomatic joints matched the pattern of uptake in our hypothesis. Dynamic ^{18}F -NaF PET-CT is a useful imaging modality for assessing painful joint prosthesis. It can differentiate between asymptomatic joints and aseptic loosening. However, more work is required for the detection of septic loosening.

Introduction

As the population ages and the average body mass index rises, lower limb arthroplasty will become more common [1]. A significant number of these patients may go on to experience pain at the site of arthroplasty at some point after surgery. Arthroplasty pain can signal biomechanical failure, peri-prosthetic infection or septic

loosening of the joint [1]. Approximately 10% of lower limb arthroplasties need surgical revision because of the pain [1].

Materials and Methods

Our patient was a 72 year old female with a painful left knee total knee replacement studied with dynamic ^{18}F -NaF PET-CT. She had underwent routine clinical and laboratory studies for the evaluation of painful prostheses, in addition to the dynamic NaF PET-CT scan. The NaF PET-CT scan was were obtained more

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than 12 months after joint replacement surgery. The interval between arthroplasty and PET-CT was 8 years. The patient gave written informed consent for the study. ¹⁸F-NaF PET-CT - Dynamic ¹⁸F-NaF PET-CT images were acquired using a GE Discovery ST with 16 slice CT (GE Healthcare®) volume imaging protocol (ViP) [2]. The patient fasted for at least 6 hours before receiving the injection. CT images of the joints were acquired, followed by dynamic PET image acquisition in list mode from the time of injection till 30 to 40 minutes after bolus intravenous administration of 250 MBq ¹⁸F NaF [2]. The images were reconstructed using ordered-subset expectation maximization, and images were corrected for attenuation.

Image Interpretation – two experienced radiologists read the studies independently, and in the case of discrepancies, a consensus was reached following discussion. When an area of increased uptake was detected in the bone-prosthesis interface of the knee arthroplasty in comparison with adjacent bone and soft tissue, the region of interest was assessed using time-activity curves with simple standardized uptake value (SUV) analysis and background subtraction [3]. Graphical interpretation was performed using our hypothesis to determine the presence of infection, aseptic loosening or neither (Figure 1). The CT images were analysed for malignment of the prosthesis.

Follow-up - The final diagnosis was made by joint aspiration and clinical follow-up for 1 year. Arthroplasties were considered infected if aspiration cultures grew organisms, if infection was clinically obvious or if microbiological samples demonstrated infection or elevated neutrophils. Arthroplasties were considered aseptic if the preceding investigations were negative and this was backed by normal C-reactive protein and erythrocyte sediment rate levels as well as a normal peripheral white cell count. Furthermore, arthroplasties that did not require surgical exploration during the follow-up period were considered uninfected.

Results

The dynamic ¹⁸F-NaF PET-CT scan correctly revealed a normal asymptomatic right knee and

aseptic loosening in the symptomatic left knee (Figure 2 a-e). The degree of uptake in the symptomatic joint exceeded background levels and also levels of uptake in the asymptomatic knee. The pattern of uptake and curve slope in both the asymptomatic and symptomatic joints matched the pattern of uptake in our hypothesis based on the understood pattern of uptake in dynamic bone scans [4] and the relatively higher degree of ¹⁸F-NaF uptake in infection [5]. There is a steeper slope and higher plateau of uptake in the symptomatic loose knee prosthesis, when compared with asymptomatic knee prostheses (Figure 2 d-e).

Discussion

¹⁸F-NaF PET-CT has been used extensively for the detection of bone metastases. However, ¹⁸F-NaF uptake is not specific for bone malignancy and increased bone uptake may occur with any other condition resulting in increased blood flow and increased bone turnover [6], hence lowering ¹⁸F-NaF specificity. ¹⁸F-NaF accumulation is well recognised in fractures and a variety of metabolic bone disease such as renal osteodystrophy, Paget's disease and fibrous dysplasia [7] as well as infection or inflammation [8]. This study demonstrates that the use of dynamic ¹⁸F-NaF for diagnosing the presence or absence of prosthetic loosening is viable. Larger multi-centre trials are required, especially to prove the role of this novel technique for the detection of peri-prosthetic infection. Pre-surgical accurate diagnosis or elimination of periprosthetic infection significantly allows clinical teams to accurately plan management [1], because current assessment methods often require the combination of clinical signs, laboratory findings and often several sequential imaging studies [9] to differentiate loosening from post-operative change and infection with an acceptable sensitivity and specificity [10]. Although the plain radiograph gives important information regarding joint stability, malrotation and malignment as well as the choice of the type of prosthesis [11]; the role of plain radiographs in the diagnosis of infection associated with prostheses is limited because of nonspecific findings common to both septic and aseptic loosening [1]. Joint aspiration or biopsy is a valuable preoperative diagnostic tool for the detection of sepsis, with a sensitivity and specificity ranging from 50% to 93%

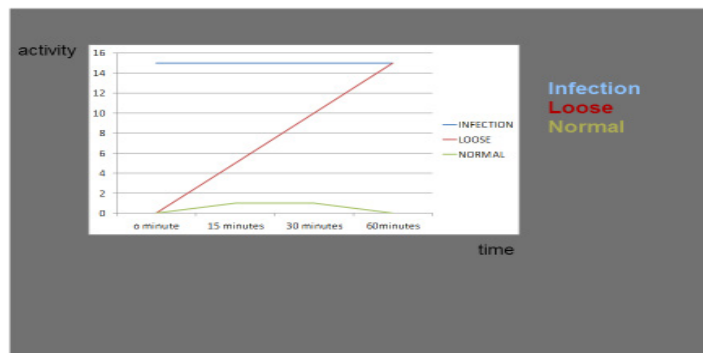


Figure 1: Sequential multiphase pattern of uptake in ¹⁸F-NaF PET-CT in the Dynamic Imaging of Joint Prostheses.

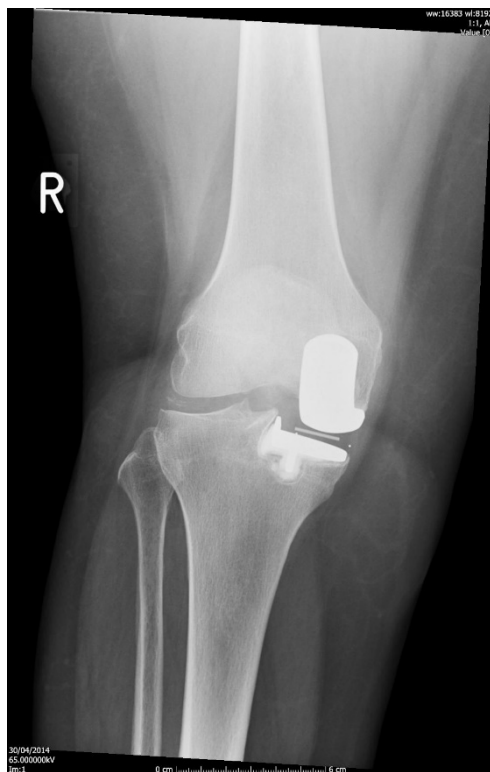


Figure 2a: Asymptomatic right knee with no osteolysis.



Figure 2b: Symptomatic left knee showing periprosthetic osteolysis.

and from 82% to 97%, respectively [1], but this degree of accuracy remains too low to exclude sepsis with certainty [1] and prior antibiotic administration may further reduce sensitivity [1]. Nuclear medicine imaging therefore has a valuable role to play in assessing joint prosthesis for infection. The 3-phase radionuclide bone scan is the most common nuclear medicine

investigation for the assessment of joint prosthesis sepsis [12]. However, the presence of orthopaedic hardware reduces the sensitivity of bone scans [10]. Two other limitations are the lengthy examination time and the cost of the examinations [1]. Sequential bone and gallium scans were the first combined studies used to diagnose osseous infection [10] and have been

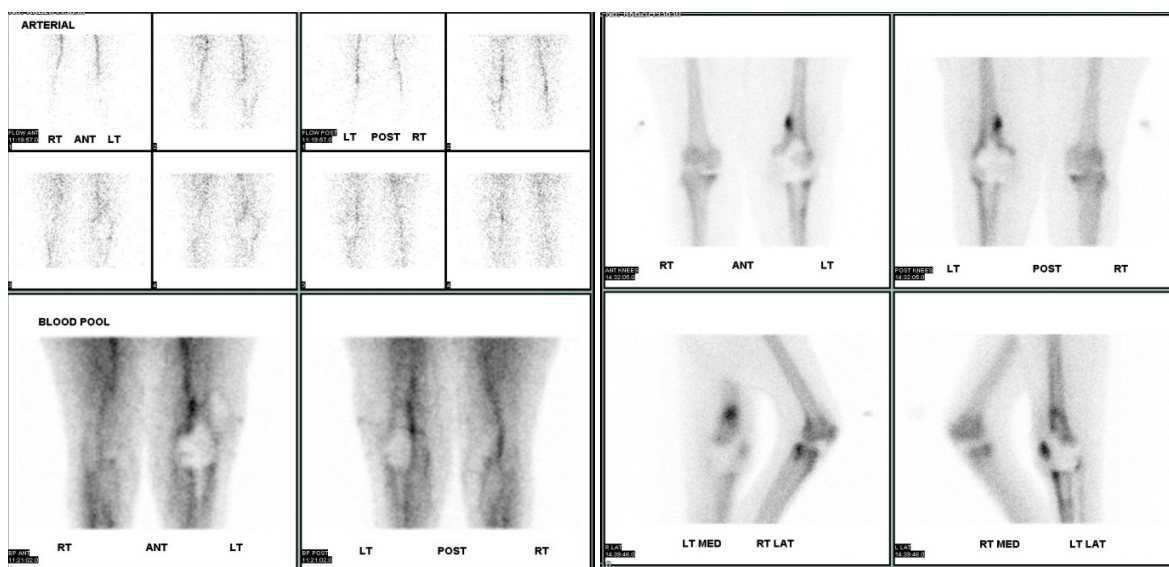


Figure 2c: Arterial & venous phase images showing minimally increased uptake in the symptomatic left knee prosthesis. Subsequent delayed phase images showing marked uptake in left femoral and tibial components in the symptomatic left knee.

applied to painful lower limb prosthesis since the 1970s [1], but are less favoured due to reported low sensitivity of 38% at the lower end of the spectrum in literature [1] or overall accuracy of 65 to 80% at the more optimistic end [10]. Other nuclear medicine studies such as ^{111}In -labeled white blood cell scanning combined with $^{99\text{m}}\text{Tc}$ -sulphur colloid bone marrow imaging has a sensitivity, specificity, and accuracy of 86%-100%, 89%-94%, and 89%-96%, respectively [1]. Disadvantages of Indium-labelled leukocyte imaging include the demanding man-hours required for vitro labelling with resultant increasing opportunities for iatrogenic errors [1] and the requirement for delayed imaging at 24 hours post-injection [1]. Occasionally, there is a requirement for additional bone marrow imaging, resulting in relatively higher radiation exposure. Attempts have been made with limited success to replace ^{111}In -labelled white cell imaging with $^{99\text{m}}\text{Tc}$ -labelled murine monoclonal antigranulocyte antibody fragments. $^{99\text{m}}\text{Tc}$ -labelled murine monoclonal antibody of the immunoglobulin bind with high affinity to CD-15 receptors present on the surface membrane of human polymorphonuclear leukocytes [13] and do not require in vitro labelling process. Antibody fragment imaging has a high negative predictive value [14], but murine antibodies have a reduced plasma half-life of few hours when compared with human IgG half-life of 3 weeks [15]. In addition, the murine IgG invokes

a HAMA response that results in faster removal of the mouse IgG, and may also result in anaphylactic hypersensitivity response [15]. The decreased circulating half-life requires increasing administered doses (which can then lead to increasing risk of HAMA, or a reduced effectiveness of the study [15]. Early attempts to justify the use of FDG PET as a single, cost-effective method of diagnosing periprosthetic infection [1,16] have since been proven to be incorrect due to false positive nonspecific peri-prosthetic uptake [17]. The cost of ^{18}F -NaF PET-CT is substantially lower than the combined costs of sequential studies comprising 2 to 3 commonly performed radionuclide scans (mainly ^{111}In -labeled white blood cell scans, bone scans and bone marrow scans) [1,18]. Furthermore, tomographic images with PET provide better spatial resolution than planar conventional nuclear medicine modalities [1], significantly improving test accuracy [1,18]. Dynamic ^{18}F -NaF PET-CT can be completed within an hour, compared with 4 hours to 2 days for other nuclear medicine methods [1].

Figure 2d, 2e shows a patient who had clear evidence of aseptic loosening. Dynamic ^{18}F -NaF PET-CT curve revealed a gentle upslope in the left prosthesis corresponding to osteolysis on the radiograph and delayed the increased uptake on the planar bone scan. The simplicity of the diagnostic criteria proposed

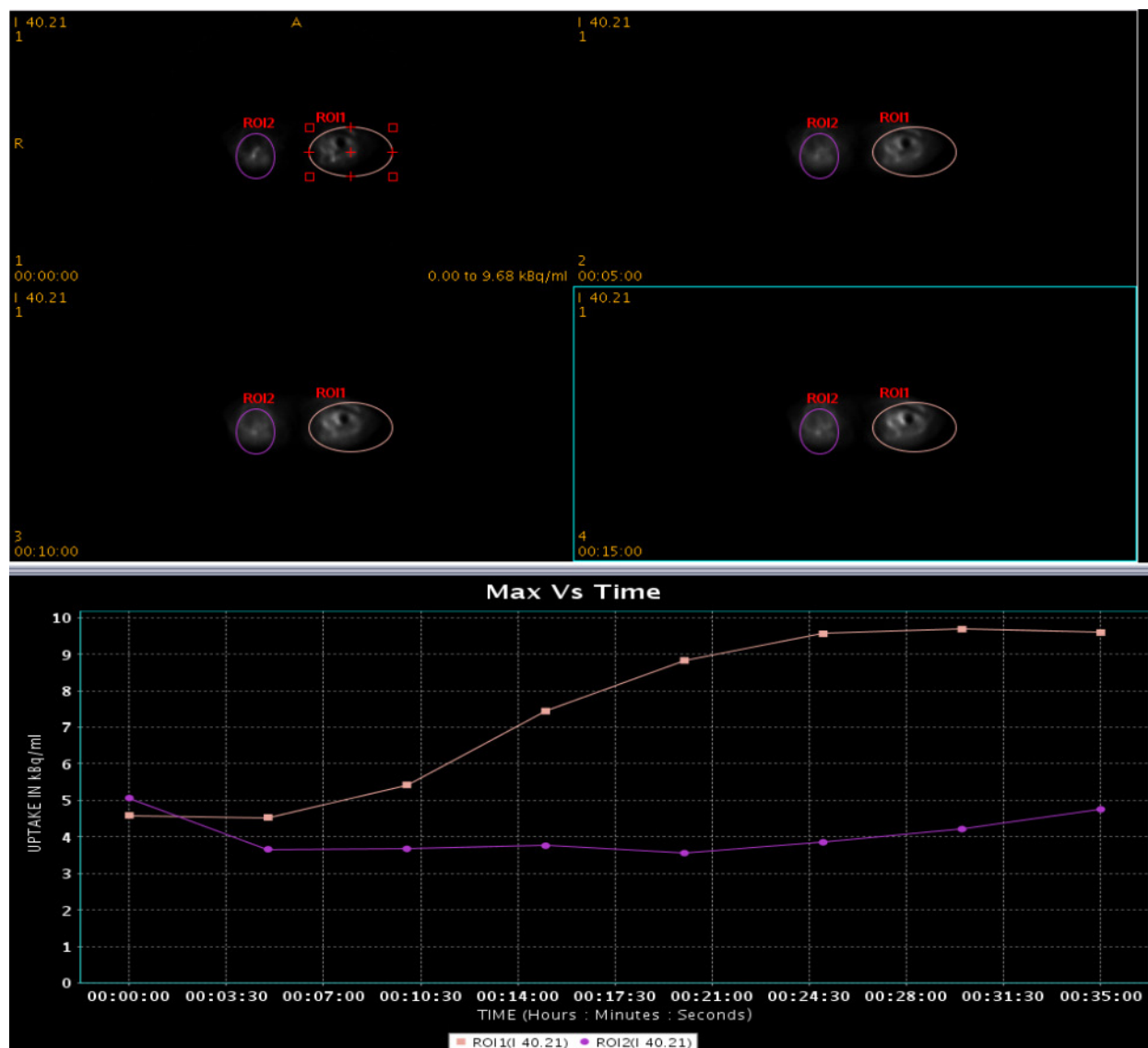


Figure 2d: NaF SUV vs sec. Symptomatic knee (pink) & asymptomatic knee (purple)

CRP, ESR, WCC and Knee aspirate all normal.
Outcome of long-term clinical follow up was loosening.

should reduce potential inter-observer variation and increase the accuracy of interpretation [19]. The interval between surgery and ^{18}F -NaF PET-CT was more than 1 year. Further research is required to confirm this proof of concept for uptake of ^{18}F -NaF in painful prosthesis as well as clearly define the appearance of infection using this promising technique. One of the major advantages of ^{18}F -NaF PET-CT over conventional nuclear medicine techniques is the simplicity of the approach and the timely availability of results within an hour [1].

Conclusion

This preliminary data demonstrates early proof of the principle that dynamic ^{18}F -NaF PET-CT can detect aseptic loosening of lower limb prosthesis and perhaps may reveal peri-prosthetic infection but has some limitations. Dynamic ^{18}F -NaF PET-CT may be more useful than 3 phase bone scans in the assessment of painful hip and knee prosthesis. Routine clinical use should not be engaged until the accuracy of dynamic

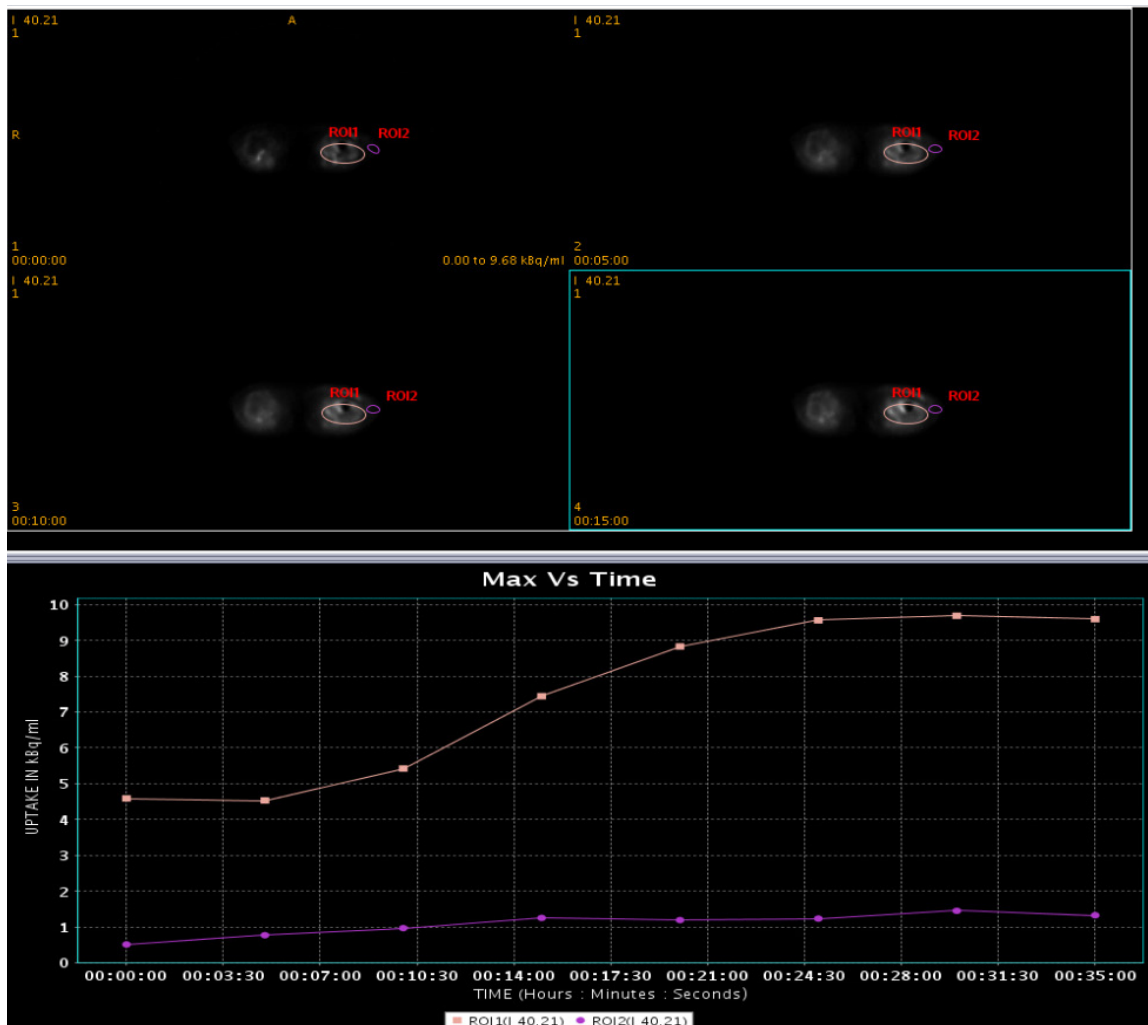


Figure 2e: Symptomatic knee (uptake (pink) & soft tissue background (purple)).

^{18}F -NaF PET-CT is fully validated. Future multi-centre research is required to establish a role for dynamic ^{18}F -NaF PET-CT for detecting aseptic loosening and septic loosening. Dynamic ^{18}F -NaF PET-CT provides quicker higher resolution images with anatomic correlation from CT. Further prospective studies using larger cohorts of patients is needed to better understand the role of dynamic ^{18}F -NaF PET-CT in diagnosing symptomatic joint prosthesis.

Acknowledgments

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